REMARKS

Claims 9-82 are now pending in the present application, of which Claims 9, 28, and 72-82 are presently withdrawn from consideration. Claims 1-8 were cancelled by previous amendment.

Claims 17-20, 29-31, and 45-47 are currently amended to recite a method for treating depression in a mammal comprising administering a therapeutically effective quantity of rotigotine.

No new matter is added, and no change in inventorship is believed to result from the present amendment.

RESPONSE TO OFFICE ACTION DATED 23 OCTOBER 2009

1. Rejection Under 35 U.S.C. §103 over 6-Way Combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler and Dinan

Claims 10-20, 27, and 29-71 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 6 documents: U.S. Patent No. 4,501,890 (Nichols) in view of Pfeiffer (2002), Drugs Aging, 19(8): 561-570 (Pfeiffer), and in further in view of U.S. Patent Publication No. 2005/0038015 (Bronzava), U.S. Patent No. 6,350,773 (Marquis), U.S. Patent No. 2003/0180332 (Rimpler), and U.S. Patent Publication No. 2005-0037983 (Dinan). This 6-way rejection is respectfully traversed.

Claim 10 is drawn to a method for treating depression in a mammal by administering a therapeutically effective quantity of rotigotine or a metabolite, prodrug or physiologically acceptable salt thereof to the mammal. Treating depression with rotigotine or salt thereof (elected species) is not obvious as there is no motivation to combine the 6 cited documents and one of ordinary skill in the art would not have had any reasonable expectation of success in treating depression with rotigotine.

1.1 No Motivation To Combine 6 Cited Documents

None of the 6 cited documents disclose or teach utilizing rotigotine in the treatment of depression. Regarding the primary document, Nichols, the Examiner (p. 3, emphasis added) admits that

> Nichols **does not teach that rotigotine treats any type of depression** (claims 10, 12-15, 32-44) in humans (claim 11) or that rotigotine is administered parenterally, transdermally or mucusally (claim 17). Nichols et al. also does not teach the amounts o[f] rotigotine to be administered (claims 18-20 and 45-59). Nichols also does not specifically teach the combination or non-combination with other pharmaceutical agents as in claims 16, 27, 29, 31, 60-71.

Bronzova, Marquis, and Dinan also fail to disclose rotigotine, much less that rotigotine is effective for the treatment of depression. Pfeiffer and Rimpler also fail to cure the deficiencies of Nichols, Bronzova, Marquis, and Dinan. Pfeiffer articulates that "rotigotine remains an unfolding story" and only discusses drugs for transdermal Parkinson's disease ("PD") treatment not depression. Rimpler does not teach or disclose employing rotigotine for the treatment of depression. Accordingly, why would one of ordinary skill in the art combine 4 documents that do not disclose rotigotine (Nichols, Bronzova, Marquis, and Dinan) with 2 documents that do not disclose depression (Pfeiffer and Rimpler)?

The Examiner (p. 4) asserts that:

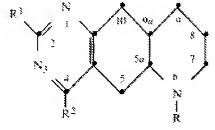
A. Nichols teaches D_2 agonists for the treatment of depression and PD;

B. Pfeiffer teaches that rotigotine is a known D_2 agonist and well tolerated for transdermal PD in humans;

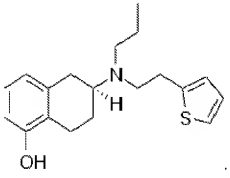
C. "Thus, since it is known that [Nichols' disclosed] D_2 agonist[s] treat both depression and Parkinson's disease, one skilled in the art would be motivated to try a known effective D_2 agonist that treats Parkinson's disease to also treat any type of depression."

Even if A and B are correct, this chain of reasoning relies on the D_2 agonists of Nichols being "similar" to rotigotine, and thus, *arguendo,* "similar" acting to those D_2 agonists of Nichols. This is not the case.

The compounds reported in Nichols are represented by the following formula:



As depicted above, the Nichols' compounds are not similar in structure in anyway to rotigotine:



Accordingly, one of ordinary skill in the art would not have had any motivation to combine Nichols, which reports very different D_2 agonists, with documents disclosing rotigotine.

The chain of reasoning also relies on the assumption that all D_2 agonists are effective in treating depression, *i.e.* knowing that a compound is a D_2 agonist (as set forth in Pfeiffer) is enough to establish its effectiveness in treating depression. Just because a drug is known to be a D_2 agonist, there is no evidence to believe it can effectively treat depression. Furthermore, just because a drug (such as rotigotine) is known to alleviate symptoms of clinical Parkinson's disease is no reason to believe it can treat depression effectively. The statement (Office Action, p. 11) that one of ordinary skill in the art would have been motivated to employ rotigotine in patients with depression can only have been made with impermissible hindsight, as the antidepressant properties of rotigotine are disclosed for the first time by Applicant in this application.

To reach a proper determination under 35 U.S.C. §103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual

information, the Examiner must then make a determination whether the claimed invention as a whole would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination. MPEP 2142. Since Applicant, for the first time provided the missing link that rotigotine is a D_2 agonist effective for treatment of depression, the Office Action's combination of 6 documents employs impermissible hindsight.

1.2 No Reasonable Expectation of Success That Rotigotine or Salts Thereof Could Treat Depression

Even if a rationale existed to select and modify elements from the 6-cited documents (which is not admitted herein), the Examiner appears to be applying the "obvious to try" standard in making the present rejection. This standard has been sanctioned by *KSR International Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), but with the proviso that there has to be "a finite number of identified, predictable solutions" (emphasis added). Furthermore, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* (emphasis added). As paraphrased in MPEP 2143.01(III), "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art."

One of ordinary skill in the art at the time of the present invention cannot have had a reasonable expectation of success, *i.e.*, could not reasonably have predicted the therapeutic effectiveness of rotigotine or salts thereof in treating depression. As discussed above, the Examiner alleges that since Nichols teaches D_2 agonists for the treatment of depression, it would have been obvious to use rotigotine, a known D_2 agonist, to treat depression. However, one of ordinary skill in the art would have had to first pick a compound considered to act on at least one dopamine receptor, then choose one that acted on at least the D_2 receptor, select D_2 agonists, and then select rotigotine. This selection process, without any pattern of preference or guidance from the cited art, would involve:

(1) Review of approximately 169 compounds that can act on dopamine receptors;

(2) Narrowing to approximately 128 compounds that are D_2 receptor acting

compounds;

(3) Selecting approximately 30 compounds that are either D_2 agonists or partial agonists;

(4) Testing at least the 30 D_2 agonists or partial agonist compounds; and

(5) Finally, choosing rotigotine to treat depression.

Accordingly, even if Nichols provides a pattern of preference for D_2 agonists, there is no pattern of preference for choosing rotigotine. At best, the very large number of possible compounds (128 D_2 acting compounds, with at least 30 being D_2 agonists or partial agonists) provides an invitation to "try" or "experiment" on the large number of D_2 agonists. The cited documents, including Nichols, provide neither guidance nor suggestion to arrive at the claimed invention or employing rotigotine to treat depression.

It was Applicant who first confirmed the antidepressant action of rotigotine. Validation of rotigotine was done using three different animal models, set forth in the specification as filed, at paragraphs **[0007]–[0014]**. In the "forced swim test" (specification as filed, Fig. 1), rotigotine led to a clear reduction in the period of immobility. In the "learned helplessness test", rotigotine at low doses improved learning behavior (specification as filed, Fig. 2). Finally, in bulbectomized rats, low doses of rotigotine reduced motor hyperactivity in a fashion similar to the antidepressant imipramine (specification as filed, Fig. 3). It is only with testing such as this, first conducted by the present inventors, that any predictability of antidepressant activity of rotigotine or salts thereof became possible. As the results of treatment by the method of Claim 10 were not predictable from the cited art, the "obvious-to-try" standard is not sufficient under *KSR, supra* to sustain a presumption of *prima facie* obviousness.

1.3 Conclusion: 6-way 35 USC §103(a) Rejection

Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 11-20, 27 and 29-71 is nonobvious over Nichols in view of Pfeiffer, and in further view of Bronzava, Marquis, Rimpler, and Dinan for at least the same reasons that Claim 10 is nonobvious.

Furthermore, the Examiner (p. 5) asserts "administering another anti-depressant would

be obvious because both compounds would be used to treat depression." The Examiner (p. 5) cited *In re Kerkhoven*, 626 F.2d 846, 850, 205, USPQ 1069, 1072 (CCPA 1980), for the proposition that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. However, unlike combining two known-effective detergents to act as a detergent, rotigotine was not known to have an antidepressant effect. For at least these reasons, a presumption of *prima facie* obviousness has not been established for Claims 27 and 60 – 71.

Withdrawal of the present 35 U.S.C. §103(a) rejection over the six-way combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler and Dinan is respectfully requested.

2 Rejection Under 35 U.S.C. §103 Over 8-Way Combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman

Claims 23-26 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 8 documents: Nichols in view of Pfeiffer, in further view of Bronzava, Marquis, Rimpler, and Dinan, and in further view of WO 02/089777 (Lauterbach) and U.S. Patent No. 4,769,028 (Hoffman). This 8-way rejection is respectfully traversed. Claims 23-26 ultimately depend from Claim 10. A presumption of *prima facie* obviousness of Claim 10 (and thus of any claim dependent therefrom) over Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman, or any combination of the 8 documents does not exist. Hoffman and Lauterbach fail to cure the deficiencies of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof (see Section 1, above). Lauterbach reports on the measured effects of rotigotine only on Parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS). Depression is only one aspect of behavior and mood included in Part I of the UPDRS. However, Lauterbach does not teach that rotigotine has effective anti-depressive properties. Even if, *arguendo,* Hoffman "teach[es] a medical plaster that releases the active agent in a matrix and comprises adhesive properties" (Office Action, p. 7), Hoffman fails to disclose or teach rotigotine or depression. Accordingly, Hoffman does not provide any teaching or expectation regarding rotigotine's effect on the treatment of depression.

Since Lauterbach and Hoffman fail to cure the deficiencies of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof, the fact remains that rotigotine was not known to have antidepressant activity prior to the present invention. Therefore, the 8 cited documents, alone or in combination, fail to establish a presumption of *prima facie* obviousness of Claim 10.

Notwithstanding the Examiner's comments with regard to Claims 23-26, each of Claims 23-26 depend from Claim 10 and are nonobvious for the same reasons Claim 10 is nonobvious over Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman or any combination thereof.

Withdrawal of the present 35 U.S.C. §103(a) rejection is respectfully requested.

3. Rejection Under 35 U.S.C. §103 Over 7-Way Combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas

Claims 21 and 22 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 7 documents: Nichols in view of Pfeiffer, in further in view of Bronzava, Marquis, Rimpler, and Dinan, and in further view of den Daas, et al. (1990) Naunyn-Schmeideberg's Arch Pharmacol, 342: 655-659 (den Daas). This 7-way rejection is respectfully traversed.

Claims 21 and 22 ultimately depend from Claim 10. A presumption of *prima facie* obviousness of Claim 10 (and thus of any claim dependent therefrom) over Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas, or any combination of the 7 documents does not exist. den Daas fails to cure the deficiencies of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof (see Section 1, above). den Daas tested 7 ester prodrugs of N-0437 for lag phase between the time of transdermal application and the onset of effects. den Daas does not disclose, teach or suggest rotigotine or the ester prodrugs to treat depression. Accordingly, den Daas does not provide any teaching regarding rotigotine's effect on the treatment of depression or provide one of ordinary skill in the art with any reasonable expectation of success of effectively treating depression with rotigotine.

Since den Daas fails to cure the deficiencies of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof, the fact remains that rotigotine was not known to

have antidepressant activity prior to the present invention. Therefore, the 7 cited documents, alone or in combination, fail to establish a presumption of *prima facie* obviousness of Claim 10.

Claim 21 recites rotigotine administered as a prodrug and Claim 22 recites that the prodrug is selected from a *Markush* group including esters, carbamate, carbonate, ketal, acetate, phosphate, phosphonate, sulfate or sulfonate. The Examiner (p. 9) states that "den Daas et al. teach[es] that prodrugs of rotigotine are active before rotigotine transdermally because the ester prodrugs are protected against metabolic attack in the skin and enter more rapidly." However, the results of the 7 esters tested in den Daas indicated that at least 4 of the esters did not have activity, and den Daas does not disclose, teach or suggest carbamate, carbonate, ketal, acetate, phosphate, phosphonate, sulfate or sulfonate prodrugs.

Notwithstanding the Examiner's comments with regard to Claims 21 and 22, each of Claims 21 and 22 depend from Claim 10 and are therefore nonobvious for at least the same reasons Claim 10 is nonbobvious over the 7-way combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas.

Withdrawal of the present 35 U.S.C. §103(a) rejection is respectfully requested.

4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.